

FOOD AND DRUG

Research LABORATORIES, INC.

MAURICE AVENUE AT 58TH STREET, MASPETH, NEW YORK 11378



FINAL

July 3, 1972

Teratologic Evaluation of FDA 71-10

(Potassium Nitrite)

in

Mice, Rats, Hamsters and Rabbits

#28

Final report-Teratologic Evaluation of FDA 71-10 (Potassium Nitrite) in Mice, Rats,
Hamsters & Rabbits
7/3/72

E23

M I C E

Food and Drug Research Laboratories
I N C O R P O R A T E D



Maurice Avenue at 58th Street
Maspeth, New York 11378

Telephone: TWining 4-0800
Cable: Foodlabs, New York

**F I N A L
R E P O R T**

Submitted to: DHEW/Public Health Service
Food and Drug Administration CA-272
5600 Fishers Lane-Room 5C-13
Rockville, Maryland 20852

Date July 3, 1972

Laboratory No. 0728 m
Contract No. FDA 71-260

Sample: Light yellow crystalline material

Marking: FDA 71-10 (Potassium nitrite)

Examination Requested: Teratologic evaluation of FDA 71-10 in mice.

Procedure: See Appendix I

Results: See Tables 1 through 4 and Appendix II

Conclusion: Subject to reexamination in the light of later findings, the following is concluded:

"The administration of up to 60 mg/kg (body weight) of the test material to pregnant mice for 10 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls."

Comment: Attention is called to the fact that this is the sixth of a series of reports which will be issued in accordance with the terms of the contract cited above. Eventually, a total of at least 36 compounds will have been tested in 18 pairs; each pair being run concurrently against one sham-treated control and one positive control group. Because of the inherent variability of biological data of the type dealt with here, the accumulation and pooling of sequential sets of control values will greatly enhance the statistical value of the findings and the ultimate reliability of the test results.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Kenneth Morgareidge
Kenneth Morgareidge, Ph.D.

Vice President

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FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 51 & 52; 57 through 60

Material: FDA 71-10

Table 1

Fate Summary
(Mice)

Date May 31, 1972

Laboratory No. 0728 m

Group	Material	Dose mg/kg	Total		At Term	
			Mated	Pregnant	Surviving (Total)	Number Pregnant
51	Sham	0	23	22	23	22
52	Aspirin*	150	32	24	30	21
57	FDA 71-10	0.3	22	20	22	20
58	FDA 71-10	1.5	25	21	25	21
59	FDA 71-10	7.0	24	23	24	23
60	FDA 71-10	32.0	28	21	28	21

* Positive Control

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group: 51 & 52; 57 through 60

Date May 31, 1972

Material: FDA 71-10

Table 2
Reproduction Data
(Mice)

Laboratory No. 0728 m

Group:	51	52	57	58	59	60
Dose (mg/kg):	Sham	Aspirin**	0.3	1.5	7.0	32.0
Pregnancies						
Total No.	22	24	20	21	23	21
Died or aborted (before Day 17)	0	3	0	0	0	0
To term (on Day 17)	22	21	20	21	23	21
Corpora lutea						
Total No.						
Average/dam mated						
Live litters						
Total No.*	22	21	20	21	23	21
Implant sites						
Total No. (at term)	268	254	248	266	276	257
Average/dam*	12.2	12.1	12.4	12.7	12.0	12.2
Resorptions						
Total No.*	18	13	12	14	14	9
Dams with 1 or more sites resorbed	8	8	8	8	9	5
Dams with all sites resorbed	0	0	0	0	0	0
Per cent partial resorptions	36.4	38.1	40.0	38.1	39.1	23.8
Per cent complete resorptions	-	-	-	-	-	-
Live fetuses						
Total No. (at term)	249	232	233	252	256	248
Average/dam*	11.3	11.0	11.7	12.0	11.1	11.8
Dead fetuses						
Total No.*	1	5	3	0	6	0
Dams with 1 or more dead	1	3	3	-	4	-
Dams with all dead	0	0	0	-	0	-
Per cent partial dead	4.55	14.3	15.0	0	17.4	-
per cent all dead	-	-	-	-	-	-
Average fetus weight, g	0.96	0.83	1.01	0.92	0.93	0.98

* Includes only those dams examined at term.

** Positive control: 150 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 51 & 52; 57 through 60

Laboratory No. 0728 m

Table 3

Material FDA 71-10

Date May 31, 1972

Summary of Skeletal Findings
(Mice)

Findings	Group No. Dose (mg/kg)	51 Sham	52 Aspirin**	57 0.3	58 1.5	59 7.0	60 32.0
Live Fetuses Examined (at term)		171/22	156/21	161/20	175/21	180/23	162/21
Sternebrae							
Incomplete oss.		45/14	52/12	37/9	45/16	63/17	39/12
Scrambled							
Bipartite		8/7	4/3		3/3		2/1
Fused							
Extra		1/1		1/1			3/1
Missing		11/4	51/8	3/2	10/6	19/9	9/4
Other							
Ribs							
Incomplete oss.							
Fused/split			3/1				
Wavy			1/1				
Less than 12				1/1			
More than 13		15/9	36/10	11/9	19/9		16/9
Other : missing			1/1				
Vertebrae							
Incomplete oss.		2/2					
Scrambled							
Fused							
Extra ctrs. oss.							
Scoliosis		2/2	1/1				2/1
Tail defects							
Other							
Skull							
Incomplete closure		4/2					
Missing							
Craniostosis							
Other: occipitals; missing			25/5				
Extremities							
Incomplete oss.		3/2	3/3				
Missing							
Extra							
Miscellaneous							
Hyoid; missing		12/10	50/3	11/7	42/14	45/16	40/14
Hyoid; reduced		23/8	27/11	7/5	30/15	17/12	25/13

* Numerator=Number of fetuses affected; Denominator=Number of litters affected

** Positive control 150 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 51 & 52; 57 through 60

Date May 31, 1972

Material FDA 71-10

Laboratory No. 0728m

Table 3-a

Summary of Soft Tissue Abnormalities
(Mice)

Group	Material	Dose level mg/kg	Dam	Number of Pups	Description
57	FDA 71-10	0.3	M 8005	1	Meningocraniocoele

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 51 & 52; 57 through 60

Date May 31, 1972

Species Mice

Table 4

Laboratory No. 0728 m

Average Body Weights*

Group	Material	Dose Level	Day					
			0	6	11	15	17	
		mg/kg						
51	Sham	0	30.2	31.0	36.0	44.6	50.6	(22)
52	Aspirin***	150	29.0	32.5	34.0	43.1	47.6	(21)
57	FDA 71-10	0.3	30.4	33.8	37.3	47.3	53.9	(20)
58	FDA 71-10	1.5	30.2	33.3	35.8	45.6	53.7	(21)
59	FDA 71-10	7.0	29.1	31.8	34.3	44.9	50.6	(23)
60	FDA 71-10	32.0	31.5	33.5	36.5	46.9	53.0	(21)

* Of pregnant dams

** Number of surviving dams in parentheses (c.f. Table 1)

*** Positive control:



Appendix I

Teratology Study in Mice

Virgin adult female albino CD-1 outbred mice were individually housed in disposable plastic cages in temperature and humidity-controlled quarters with free access to food and fresh tap water. They were mated with young adult males, and observation of the vaginal sperm plug was considered Day 0 of gestation. Beginning on Day 6 and continuing daily through Day 15 of gestation, the females were dosed with the indicated dosages by oral intubation; the controls were sham treated.

Body weights were recorded on Days 0, 6, 11, 15, and 17 of gestation. All animals were observed daily for appearance and behavior with particular attention to food consumption and weight, in order to rule out any abnormalities which may have occurred as a result of anorexic effects in the pregnant female animal.

On Day 17 all dams were subjected to Caesarean section under surgical anesthesia, and the numbers of implantation sites, resorption sites, and live and dead fetuses were recorded. The body weights of the live pups were also recorded. The urogenital tract of each dam was examined in detail for anatomical normality.

All fetuses were examined grossly for the presence of external congenital abnormalities. One-third of the fetuses of each litter underwent detailed visceral examinations employing 10X magnification. The remaining two-thirds were cleared in potassium hydroxide (KOH), stained with alizarin red S dye and examined for skeletal defects.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 51

Appendix II

Date May 31, 1972

Material Sham

Reproduction Data in Mice (Individual)

Laboratory No. 0728

Dose 0

Dam No.	Fate *	Implant Sites	Fetuses		Resorption Sites	Average Fetus Weight (g)	Remarks
			Alive	Dead			
S 8151	P	11	10		1	0.96	
S 8152	P	12	12			1.35	
S 8153	P	12	12			0.87	
S 8154	NP	0				----	
S 8155	P	11	11			1.13	
S 8156	P	13	13			1.01	
S 8157	P	11	11			1.11	
S 8158	P	12	12			1.02	
S 8159	P	14	12		2	1.05	
S 8160	P	15	12	1	2	0.87	
S 8161	P	12	12			1.00	
S 8162	P	14	14			0.86	
S 8163	P	13	12		1	0.93	
S 8164	P	11	10		1	0.85	
S 8165	P	12	12			1.02	
S 8166	P	13	13			0.95	
S 8167	P	11	11			0.97	
S 8168	P	14	14			1.00	
S 8169	P	12	10		2	1.01	
S 8170	P	12	12			1.01	
S 8171	P	11	3		8	0.80	
S 8172	P	10	9		1	0.73	
S 8173	P	12	12			0.68	

* P= Pregnant; NP= Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 52

Appendix II

Date May 31, 1972

Material Aspirin

Reproduction Data in Mice (Individual)

Laboratory No. 0728

Dose 150 mg/kg

Dam No.	Fate *	Implant Sites	Fetuses		Resorption Sites	Average Fetus Weight (g)	Remarks
			Alive	Dead			
A 8151	P	14			14	----	Died Day 14.
A 8152	P	13	9		4	0.88	
A 8153	P	14	13		1	0.66	
A 8154	P	13			13	----	Died Day 15
A 8155	P	14	10		4	0.77	
A 8156	P	14	14			0.71	
A 8157	P	11	11			0.83	
A 8158	P	10	10			0.65	
A 8159	-	-				----	Not assigned.
A 8160	NP	0				----	
A 8161	P	11	10		1	0.85	
A 8162	P	13	13			0.93	
A 8163	P	15	13	2		1.00	
A 8164	-	-				----	Not assigned.
A 8165	P	10	10			1.12	
A 8166	NP	0				----	
A 8167	P	12		12		----	Died Day 16
A 8168	P	13	13			0.95	
A 8169	NP	0				----	
A 8170	NP	0				----	
A 8171	P	15	12	2	1	0.62	
A 8172	NP	0				----	
A 8173	NP	0				----	
A 8174	P	13	12		1	0.63	
A 8175	NP	0				----	
A 8176	NP	0				----	
A 8177	P	14	12		2	0.48	
A 8178	P	14	10	1	3	0.77	
A 8179	P	12	12			0.90	
A 8180	P	12	12			0.86	
A 8180 I	P	13	13			0.99	
A 8180 II	P	9	9			0.61	
A 8180 III	P	12	12			1.15	
A 8180 IV	P	2	2			1.15	

* P= Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 57

Appendix II

Date May 31, 1972

Material FDA 71-10

Reproduction Data in Mice (Individual)

Laboratory No. 0728 m

Dose 0.3 mg/kg

Dam No.	Fate *	Implant Sites	Fetuses		Resorption Sites	Average Fetus Weight (g)	Remarks
			Alive	Dead			
M 8001	P	11	11			1.03	
M 8002	P	14	12		2	0.97	
M 8003	P	12	12			0.95	
M 8004	P	1	1			1.51	
M 8005	P	11	10	1		1.09	
M 8006	P	16	16			1.00	
M 8007	P	12	11		1	0.90	
M 8008	P	15	14	1		1.09	
M 8009	P	11	11			1.13	
M 8010	P	14	13		1	1.06	
M 8011	P	16	14		2	0.77	
M 8012	P	13	13			0.80	
M 8013	P	12	12			1.02	
M 8014	P	13	12		1	1.06	
M 8015	P	13	12		1	1.02	
M 8016	P	10	6	1	3	1.16	
M 8017	P	14	14			0.89	
M 8018	P	14	13		1	1.02	
M 8019	NP	0				----	
M 8020	NP	0				----	
M 8021	P	13	13			0.89	
M 8022	P	13	13			0.88	

* P= Pregnant; NP= Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 58

Appendix II

Date May 31, 1972

Material FDA 71-10

Reproduction Data in Mice (Individual)

Laboratory No: 0728 m

Dose 1.5 mg/kg

Dam No.	Fate *	Implant Sites	Fetuses		Resorption Sites	Average Fetus Weight (g)	Remarks
			Alive	Dead			
M 8031	P	17	17			0.88	
M 8032	P	11	10		1	1.08	
M 8033	P	13	13			0.99	
M 8034	P	15	14		1	0.77	
M 8035	P	11	11			0.90	
M 8036	P	15	15			0.93	
M 8037	P	11	9		2	1.08	
M 8038	P	15	14		1	1.05	
M 8039	P	14	14			1.04	
M 8040	P	10	10			0.84	
M 8041	NP	0				----	
M 8042	NP	0				----	
M 8043	P	13	12		1	0.86	
M 8044	NP	0				----	
M 8045	P	12	12			0.86	
M 8046	P	11	11			0.98	
M 8047	NP	0				----	
M 8048	P	12	11		1	0.89	
M 8049	P	12	12			0.81	
M 8050	P	18	17		1	0.78	
M 8051	P	15	9		6	0.65	
M 8052	P	12	12			0.97	
M 8053	P	8	8			0.85	
M 8054	P	11	11			1.01	
M 8055	P	10	10			1.06	

* P= Pregnant; NP= Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 59

Appendix II

Date May 31, 1972

Material FDA 71-10

Reproduction Data in Mice (Individual)

Laboratory No. 0728 m

Dose 7.0 mg/kg

Dam No.	Fate *	Implant Sites	Fetuses		Resorption Sites	Average Fetus Weight (g)	Remarks
			Alive	Dead			
M 8061	P	14	14			0.89	
M 8062	P	14	14			0.98	
M 8063	P	12	11		1	0.88	
M 8064	P	12	11		1	1.15	
M 8065	P	11	10		1	1.11	
M 8066	P	13	13			1.08	
M 8067	P	14	11		3	0.91	
M 8068	P	15	14		1	0.90	
M 8069	P	8	8			1.04	
M 8070	P	13	13			0.95	
M 8071	P	11	11			1.00	
M 8072	P	12	12			0.87	
M 8073	P	13	13			0.98	
M 8074	P	9	9			0.99	
M 8075	P	13	13			0.90	
M 8076	P	13	13			0.97	
M 8077	P	13	9	2	2	0.83	
M 8078	P	10	8	2		0.79	
M 8079	P	11	9		2	0.78	
M 8080	P	14	13		1	0.93	
M 8081	P	9	9			0.71	
M 8082	P	12	9	1	2	0.90	
M 8083	NP	0				----	
M 8084	P	10	9	1		0.80	

* P= Pregnant; NP= Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 60
 Material FDA 71-10
 Dose 32.0 mg/kg

Appendix II

Reproduction Data in Mice (Individual)

Date May 31, 1972
 Laboratory No. 0728 m

Dam No.	Fate *	Implant Sites	Fetuses		Resorption Sites	Average Fetus Weight (g)	Remarks
			Alive	Dead			
M 8091	P	13	13			0.93	
M 8092	NP	0				----	
M 8093	P	12	12			0.98	
M 8094	P	13	13			0.96	
M 8095	NP	0				----	
M 8096	P	16	16			1.24	
M 8097	P	12	9		3	1.20	
M 8098	P	10	10			1.06	
M 8099	P	13	11		2	0.86	
M 8100	P	10	10			0.78	
M 8101	P	14	13		1	0.95	
M 8102	NP	0				----	
M 8103	P	12	12			0.97	
M 8104	P	13	13			0.96	
M 8105	P	13	12		1	0.85	
M 8106	P	13	13			0.93	
M 8107	P	12	12			0.96	
M 8108	NP	0				----	
M 8109	NP	0				----	
M 8110	NP	0				----	
M 8111	NP	0				----	
M 8112	P	14	14			0.61	
M 8113	P	10	10			1.00	
M 8114	P	10	10			0.80	
M 8115	P	13	11		2	1.34	
M 8116	P	13	13			0.88	
M 8117	P	11	11			1.20	
M 8118	P	10	10			1.05	

* P= Pregnant; NP= Not Pregnant

R A T S

Food and Drug Research Laboratories
INCORPORATED



Maurice Avenue at 58th Street
Maspeth, New York 11378
Telephone: TWining 4-0800
Cable: Foodlabs, New York

**FINAL
REPORT**

Submitted to: DHEW/Public Health Service
Food and Drug Administration CA-272
5600 Fishers Lane-Room 5C-13
Rockville, Maryland 20852

Date July 3, 1972

Laboratory No. 0729 m
Contract No. FDA 71-260

Sample: Light yellow crystalline material

Marking: FDA 71-10 (Potassium nitrite)

Examination Requested: Teratologic evaluation of FDA 71-10 in rats


Procedure: See Appendix I

Results: See Tables 1 through 4 and Appendix II

Conclusion: Subject to reexamination in the light of later findings, the following is concluded:

"The administration of up to 3.0 mg/kg (body weight) of the test material to pregnant rats for 10 consecutive days had no discernible effect on nidation, or on maternal or fetal survival. At this dose level, the number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls. However, at a dose level of 10.0 mg/kg (body weight), there were slight indications of delayed skeletal maturation, particularly with respect to ribs and skull. Outright increase in terata were not observed nor did this dose cause any alteration in nidation or fetal survival. It was concluded that this test material is not a frank teratogen for the rat under the experimental conditions employed."

FOOD AND DRUG RESEARCH LABORATORIES, INC.


Kenneth Morgareidge, Ph.D.
Vice President

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Comment: Attention is called to the fact that this is the sixth of a series of reports which will be issued in accordance with the terms of the contract cited above. Eventually, a total of at least 36 compounds will have been tested in 18 pairs; each pair being run concurrently against one sham-treated control and one positive control group. Because of the inherent variability of biological data of the type dealt with here, the accumulation and pooling of sequential sets of control values will greatly enhance the statistical value of the findings and the ultimate reliability of the test results.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 51 & 52: 57 through 60

Material: FDA 71-10

Table 1

Fate Summary
(Rats)

Date May 31, 1972

Laboratory No. 0729 m

Group	Material	Dose mg/kg	Total		At Term	
			Mated	Pregnant	Surviving (Total)	Number Pregnant
51	Sham.	0	22	21	22	21
52	Aspirin*	250	22	22	22	22
57	FDA 71-10	0.1	23	23	23	23
58	FDA 71-10	0.5	23	20	23	20
59	FDA 71-10	3.0	22	22	22	22
60	FDA 71-10	10.0	23	21	22	21

* Positive Control

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group: 51 & 52; 57 through 60

Date May 31, 1972

Material: FDA 71-10

Table 2
Reproduction Data

Laboratory No. 0729 m

(Rats)

Group:	51	52	57	58	59	60
Dose (mg/kg):	Sham	Aspirin**	0.1	0.5	3.0	10.0
Pregnancies						
Total No.	21	22	23	20	22	21
Died or aborted (before Day 20)	0	0	0	0	0	1
To term (on Day 20)	21	22	23	20	22	21
Corpora lutea						
Total No.						
Average/dam mated						
Live litters						
Total No.*	21	10	22	20	22	21
Implant sites						
Total No. (at term)	229	239	252	231	251	238
Average/dam*	10.9	10.9	11.0	11.6	11.4	11.3
Resorptions						
Total No.*	15	144	24	5	8	4
Dams with 1 or more sites resorbed	6	18	12	4	7	3
Dams with all sites resorbed	0	12	1	0	0	0
Per cent partial resorptions	28.6	81.8	52.2	20.0	31.8	14.3
Per cent complete resorptions	0	54.5	4.35	-	-	-
Live fetuses						
Total No. (at term)	214	92	228	226	243	234
Average/dam*	10.2	4.18	9.91	11.3	11.0	11.1
Dead fetuses						
Total No.*	0	3	0	0	0	0
Dams with 1 or more dead	-	2	-	-	-	-
Dams with all dead	-	0	-	-	-	-
Per cent partial dead	-	9.09	-	-	-	-
per cent all dead	-	-	-	-	-	-
Average fetus weight, g	3.75	2.19	3.90	3.87	4.06	3.82

* Includes only those dams examined at term.

** Positive control: 250 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 51 & 52; 57 through 60

Laboratory No. 0729 m

Table 3

Material FDA 71-10

Date May 31, 1972

Summary of Skeletal Findings
(Rats)

Findings	Group No. Dose (mg/kg)	51 Sham	52 ** Aspirin	53 0.1	54 0.5	55 3.0	56 10.0
Live Fetuses Examined (at term)		215/21	52/9a	228/22	226/20	242/22	235/21
Sternebrae							
Incomplete oss.		11/8	38/9	13/8	9/7	11/5	16/7
Scrambled				1/1			1/1
Bipartite							
Fused							
Extra				1/1		3/1	4/2
Missing							
Other							
Ribs							
Incomplete oss.			5/3				
Fused/split			11/5				
Wavy	4/4		26/8	9/6	11/5	5/3	10/5
Less than 12			3/3				
More than 13			12/7				
Other							
Vertebrae							
Incomplete oss.		2/2	40/7	1/1	1/1	1/1	1/1
Scrambled							
Fused			1/1				
Extra ctrs. oss.							
Scoliosis			3/3				
Tail defects							
Other							
Skull							
Incomplete closure		8/5	44/9	9/8	8/5	13/5	21/5
Missing							
Craniostosis							
Other							
Extremities							
Incomplete oss.		1/1	1/1				
Missing							
Extra							
Miscellaneous							
Hyoid; missing		4/2	44/9	6/5	6/5	10/6	6/6
Hyoid; reduced		3/2	1/1			5/5	4/3

* Numerator=Number of fetuses affected; Denominator=Number of litters affected.

** Positive control at 250 mg/kg

a.) One litter lost

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 51 & 52; 57 through 60Date May 31, 1972Material FDA 71-10Laboratory No. 0729m

Table 3-a

Summary of Soft Tissue Abnormalities
(Rats)

Group	Material	Dose level mg/kg	Dam	Number of Pups	Description
51	Sham	0	S 9153	1	Cervical subcutaneous hematoma
			S 9154	1	Cervical subcutaneous hematoma
			S 9155	2	Cervical subcutaneous hematoma
			S 9156	1	Cervical subcutaneous hematoma
52	Aspirin	250	A 9152	2 1	Enterohepatocoele Acrania, spina bifida
			A 9161	3	Acrania, spina bifida
			A 9162	2	Acrania, spina bifida
			A 9168	1	Acrania, spina bifida, craniocoele
			A 9170	3 1	Acrania Spina bifida
58	FDA 71-10	3.0	M 9038	1	Thoracic subcutaneous hematoma
			M 9045	1	Thoracic subcutaneous hematoma

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 51 & 52: 57 through 60

Date May 31, 1972

Species Rats

Table 4

Laboratory No. 0729 m

Average Body Weights*

Group	Material	Dose Level mg/kg	-----Day-----					
			0	6	11	15	20	**
			-----g-----					
51	Sham	0	203	219	239	266	330	(21)
52	Aspirin***	250	205	224	242	261	293	(22)
57	FDA 71-10	0.1	211	225	251	272	340	(23)
58	FDA 71-10	0.5	201	218	240	266	333	(20)
59	FDA 71-10	3.0	211	230	253	279	348	(22)
60	FDA 71-10	10.0	206	223	245	270	333	(21)

* Of pregnant dams

** Number of surviving dams in parentheses (c.f. Table 1)

*** Positive control:



Appendix I

Teratology Study in Rats

Virgin adult female albino rats (Wistar derived stock) were individually housed in mesh bottom cages in temperature and humidity-controlled quarters with free access to food and fresh tap water. They were mated with young adult males, and observation of the vaginal sperm plug was considered Day 0 of gestation. Beginning on Day 6 and continuing daily through Day 15 of gestation, the females were dosed with the indicated dosages by oral intubation; the controls were sham treated.

Body weights were recorded on Days 0, 6, 11, 15, and 20 of gestation. All animals were observed daily for appearance and behavior with particular attention to food consumption and weight, in order to rule out any abnormalities which may have occurred as a result of anorexic effects in the pregnant female animal.

On Day 20 all dams were subjected to Caesarean section under surgical anesthesia, and the numbers of implantation sites, resorption sites, and live and dead fetuses were recorded. The body weights of the live pups were also recorded. The urogenital tract of each dam was examined in detail for anatomical normality.

All fetuses were examined grossly for the presence of external congenital abnormalities. One-third of the fetuses of each litter underwent detailed visceral examinations employing 10X magnification. The remaining two-thirds were cleared in potassium hydroxide (KOH), stained with alizarin red S dye and examined for skeletal defects.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Date May 31, 1972

Group 57

Material FDA 71-10

Reproduction Data in Rats (Individual)

Laboratory No. 0729 m

Dose 0.1 mg/kg

Dam No.	Fate*	Implant Sites	Fetuses		Resorption Sites	Average Fetus Weight (g)	Remarks
			Alive	Dead			
M 9001	P	11	10		1	4.0	
M 9002	P	8	7		1	3.3	
M 9003	P	11	6		5	5.5	
M 9004	P	8	8			4.4	
M 9005	P	14	13		1	4.2	
M 9006	P	12	12			4.0	
M 9007	P	13	13			3.7	
M 9008	P	11	11			3.9	
M 9009	P	13	13			3.8	
M 9010	P	9	9			3.9	
M 9011	P	9	8		1	3.7	
M 9012	P	16	15		1	3.8	
M 9013	P	12	11		1	3.2	
M 9014	P	11	11			3.8	
M 9015	P	11	11			4.5	
M 9016	P	12	10		2	3.8	
M 9017	P	10	10			3.8	
M 9018	P	9	8		1	4.2	
M 9019	P	12	12			4.0	
M 9020	P	16	15		1	3.8	
M 9021	P	11	11			3.8	
M 9022	P	1			1	---	
M 9023	P	12	4		8	2.7	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 58

Appendix II

Date May 31, 1972

Material FDA 71-10

Reproduction Data in Rats (Individual)

Laboratory No. 0729 m

Dose 0.5 mg/kg

Dam No.	Fate*	Implant Sites	Fetuses		Resorption Sites	Average Fetus Weight (g)	Remarks
			Alive	Dead			
M 9031	P	10	10			4.0	
M 9032	P	13	13			4.1	
M 9033	NP					---	
M 9034	P	10	10			3.6	
M 9035	P	11	11			3.8	
M 9036	NP					---	
M 9037	P	13	13			3.9	
M 9038	P	13	13			3.7	
M 9039	P	13	12		1	3.5	
M 9040	P	10	8		2	3.9	
M 9041	P	11	11			3.8	
M 9042	P	10	10			4.0	
M 9043	P	11	11			3.8	
M 9044	P	13	13			3.8	
M 9045	P	11	11			4.2	
M 9046	P	12	12			4.3	
M 9047	P	9	8		1	4.1	
M 9048	P	12	11		1	3.6	
M 9049	P	11	11			3.8	
M 9050	P	12	12			3.9	
M 9051	NP					---	
M 9052	P	13	13			3.7	
M 9053	P	13	13			3.9	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Date May 31, 1972

Group 59

Material FDA 71-10

Reproduction Data in Rats (Individual)

Laboratory No. 0729 m

Dose 3.0 mg/kg

Dam No.	Fate*	Implant Sites	Fetuses		Resorption Sites	Average Fetus Weight (g)	Remarks
			Alive	Dead			
M 9061	P	11	10		1	5.4	
M 9062	P	8	8			4.2	
M 9063	P	12	11		1	2.5	
M 9064	P	3	3			4.2	
M 9065	P	11	11			3.9	
M 9066	P	11	11			3.9	
M 9067	P	11	11			4.3	
M 9068	P	14	14			4.0	
M 9069	P	13	13			4.0	
M 9070	P	12	11		1	4.0	
M 9071	P	12	12			3.8	
M 9072	P	12	10		2	4.2	
M 9073	P	11	11			4.0	
M 9074	P	9	9			4.1	
M 9075	P	11	11			4.5	
M 9076	P	12	12			4.0	
M 9077	P	13	13			4.0	
M 9078	P	10	9		1	4.0	
M 9079	P	15	15			4.2	
M 9080	P	13	13			4.0	
M 9081	P	14	13		1	4.0	
M 9082	P	13	12		1	4.2	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 60

Appendix II

Date May 31, 1972

Material FDA 71-10

Reproduction Data in Rats (Individual)

Laboratory No. 0729 m

Dose 10.0 mg/kg

Dam No.	Fate*	Implant Sites	Fetuses		Resorption Sites	Average Fetus Weight (g)	Remarks
			Alive	Dead			
M 9091	P	11	11			4.2	
M 9092	NP					---	
M 9093	P	11	11			2.5	
M 9094	P	14	13		1	3.9	
M 9095	P	12	12			4.1	
M 9096	P	13	13			3.6	
M 9097	P	10	10			4.1	
M 9098	P	13	13			3.4	
M 9099	P	10	10			4.1	
M 9100	P	12	12			3.8	
M 9101	P	13	13			3.8	
M 9102	NP					---	SM Died Day 20 (respiratory)
M 9103	P	12	10		2	4.0	
M 9104	P	13	13			4.0	
M 9105	P	10	10			3.9	
M 9106	P	12	12			4.0	
M 9107	P	9	9			3.9	
M 9108	P	14	14			3.7	
M 9109	P	4	4			4.0	
M 9110	P	12	12			4.0	
M 9111	P	11	11			4.0	
M 9112	P	11	10		1	3.7	
M 9113	P	11	11			3.6	

* P = Pregnant; NP = Not Pregnant

HAMSTERS

Food and Drug Research Laboratories
INCORPORATED



Maurice Avenue at 58th Street
Maspeth, New York 11378

Telephone: TWining 4-0800

Cable: Foodlabs, New York

**FINAL
REPORT**

Submitted to: DHEW/Public Health Service
Food and Drug Administration CA-272
5600 Fishers Lane-Room 5C-13
Rockville, Maryland 20852

Date July 3, 1972

Laboratory No. 0730 m
Contract No. FDA 71-260

Sample: Light yellow crystalline material

Marking: FDA 71-10 (Potassium nitrite)

Examination Requested: Teratologic evaluation of FDA 71-10 in hamsters

Procedure: See Appendix I

Results: See Tables 1 through 4 and Appendix II

Conclusion: Subject to reexamination in the light of later findings, the following is concluded:

"The administration of up to 32 mg/kg (body weight) of the test material to pregnant hamsters for 5 consecutive days had no effect on nidation, or on maternal or fetal survival. The number of abnormalities occurring in soft tissues of fetuses from the test groups did not differ from the number seen in the sham-treated controls. However, the administration of this test material appeared to be associated with delayed skeletal maturation in this species which was not clearly dose-related. Whether or not the substance is teratogenic in the hamster can only be determined on the basis of further studies."

FOOD AND DRUG RESEARCH LABORATORIES, INC.


Kenneth Morgareidge, Ph.D.

Vice President

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Comment: Attention is called to the fact that this is the sixth of a series of reports which will be issued in accordance with the terms of the contract cited above. Eventually, a total of at least 36 compounds will have been tested in 18 pairs; each pair being run concurrently against one sham-treated control and one positive control group. Because of the inherent variability of biological data of the type dealt with here, the accumulation and pooling of sequential sets of control values will greatly enhance the statistical value of the findings and the ultimate reliability of the test results.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 51 & 52; 57 through 60.

Material: FDA 71-10

Table 1

Fate Summary
(Hamsters)

Date May 31, 1972

Laboratory No. 0730 m

Group	Material	Dose mg/kg	Total		At Term	
			Mated	Pregnant	Surviving (Total)	Number Pregnant
51	Sham	0	24	21	24	21
52	Aspirin*	250	23	22	23	22
57	FDA 71-10	0.3	22	22	22	22
58	FDA 71-10	1.5	24	23	23	23
59	FDA 71-10	7.0	23	21	23	21
60	FDA 71-10	32	26	21	25	21

* Positive Control

Group: 51 & 52; 57 through 60

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Date May 31, 1972Material: FDA 71-10Table 2
Reproduction DataLaboratory No. 0730 m

(Hamsters)

Group:	51	52	57	58	59	60.
Dose (mg/kg):	Sham	Aspirin**	0.3	1.5	7.0	32
Pregnancies						
Total No.	21	22	22	23	21	21
Died or aborted (before Day 14)	0	0	0	0	0	0
To term (on Day 14)	21	22	22	23	21	21
Corpora lutea						
Total No.						
Average/dam mated						
Live litters						
Total No.*	21	22	22	23	21	21
Implant sites						
Total No. (at term)	255	271	257	292	255	250
Average/dam*	12.1	12.3	11.7	12.7	12.1	11.9
Resorptions						
Total No.*	11	9	11	11	9	18
Dams with 1 or more sites resorbed	8	7	9	9	7	10
Dams with all sites resorbed	0	0	0	0	0	0
Per cent partial resorptions	38.1	31.8	40.9	39.1	33.3	47.6
Per cent complete resorptions	-	-	-	-	-	-
Live fetuses						
Total No. (at term)	243	262	243	278	245	232
Average/dam*	11.6	11.9	11.0	12.1	11.7	11.0
Dead fetuses						
Total No.*	1	0	3	3	1	0
Dams with 1 or more dead	1	-	2	3	1	0
Dams with all dead	0	-	0	0	0	0
Per cent partial dead	4.76	-	9.09	13.0	4.76	-
per cent all dead	-	-	-	-	-	-
Average fetus weight, g	1.87	1.74	1.80	1.82	1.86	1.83

* Includes only those dams examined at term.

** Positive control: 250 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 51 & 52; 57 through 60Laboratory No. 0730 m

Table 3

Material FDA 71-10Date May 31, 1972Summary of Skeletal Findings
(Hamsters)

Findings	Group No. Dose (mg/kg)	51 Sham	52 Aspirin**	57 0.3	58 1.5	59 7.0	60 32.0
Live Fetuses Examined (at term)		166/21	183/22	166/22	193/23	170/21	160/21
Sternebrae							
Incomplete oss.		106/21	124/22	111/22	125/23	98/21	103/21
Scrambled							
Bipartite		56/17	91/21	55/20	84/23	68/19	56/20
Fused							
Extra		8/6	1/1	1/1	4/3	8/6	3/2
Missing		27/14	84/16	55/21	46/18	34/15	49/19
Other							
Ribs							
Incomplete oss.							
Fused/split			1/1			2/1	
Wavy					1/1		
Less than 12							
More than 13		17/9	33/15	21/14	32/14	38/15	28/12
Other							
Vertebrae							
Incomplete oss.			3/2				
Scrambled			4/2				
Fused							
Extra ctrs. oss.		1/1	2/1				
Scoliosis		1/1	7/4	1/1	20/8	8/5	9/6
Tail defects							
Other							
Skull							
Incomplete closure		1/1	5/2			1/1	3/3
Missing							
Craniostosis							
Other; Exencysholy					1/1		
Extremities							
Incomplete oss.		3/1	26/10				
Missing							
Extra							
Miscellaneous							
Hyoid; reduced		1/1	7/4		2/1		
Hyoid; missing			11/4			1/1	

* Numerator=Number of fetuses affected; Denominator=Number of litters affected
 ** Positive control at 250 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 51 & 52; 57 through 60

Date May 31, 1972

Material FDA 71-10

Laboratory No. 0730m

Table 3-a
Summary of Soft Tissue Abnormalities
(Hamsters)

Group	Material	Dose level mg/kg	Dam	Number of Pups	Description
59	FDA 71-10	7.0	M 0075	2	Cranial subcutaneous hematoma

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 51 & 52, 57 through 60

Species Hamsters

Table 4

Average Body Weights

Date May 31, 1972

Laboratory No. 0730 m

Group	Material	Dose Level mg/kg	Day				
			0	6	8	10	14**
51	Sham	0	97.3	101.4	105.8	115.2	138.5 (21)
52	Aspirin***	250	97.7	102.9	104.3	114.7	137.3 (22)
57	FDA 71-10	0.3	92.5	101.1	103.6	113.4	135.9 (22)
58	FDA 71-10	1.5	96.1	99.8	103.6	113.5	133.1 (23)
59	FDA 71-10	7.0	95.5	100.1	102.9	113.5	136.1 (21)
60	FDA 71-10	32.0	99.8	105.2	106.9	115.7	138.7 (21)

* Of pregnant dams

** Number of surviving dams in parentheses (c.f. Table 1)

*** Positive control:



Appendix I

Teratology Study in Hamsters

Virgin adult female golden hamsters from an outbred strain were individually housed in mesh bottom cages in temperature and humidity controlled quarters with free access to food and fresh tap water at all times. They were mated (1 to 1) with mature males and the appearance of motile sperm in the vaginal smear was considered as Day 0 of gestation. Beginning on Day 6 and continuing daily through Day 10 of gestation, the indicated dose levels of the test material were administered by oral intubation; the controls were sham-treated.

Body weights were recorded on Days 0, 8, 10, and 14 of the gestation period. All animals were observed daily for appearance and behavior with particular attention to food consumption in order to better recognize any abnormalities resulting from anorexic effects in the pregnant animal.

On Day 14, all animals were subjected to Caesarian section under deep anesthesia and the numbers of implantation sites, resorption sites, live and dead fetuses were recorded. All live pups were weighed and the genital tract of each dam was examined for any anatomical abnormalities.

All fetuses were examined grossly for the presence of external congenital defects and one-third of each litter underwent detailed visceral examination under 10X magnification. The remaining two-thirds of the pups were cleared in potassium hydroxide, stained with alizarin red dye, and examined for the presence of skeletal abnormalities.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 51

Appendix II

Date May 31, 1972

Material Sham

Reproduction Data in Hamsters (Individual)

Laboratory No. 0730

Dose 0

Dam No.	Fate*	Implant Sites	Fetuses		Resorption Sites	Average Fetus Weight (g)	Remarks
			Alive	Dead			
S 0151	P	9	9			1.59	
S 0152	P	12	12			1.93	
S 0153	P	14	14			1.67	
S 0154	P	14	12	1	1	1.81	
S 0155	P	12	12			2.00	
S 0156	P	11	10		1	1.89	
S 0157	P	11	11			1.90	
S 0158	P	13	13			1.73	
S 0159	P	10	10			2.23	
S 0160	NP					----	
S 0161	P	13	12		1	1.48	
S 0162	NP					----	
S 0163	P	14	13		1	1.93	
S 0164	P	14	11		3	2.04	
S 0165	P	10	10			1.73	
S 0166	P	15	15			1.83	
S 0167	P	11	10		1	1.89	
S 0168	P	11	9		2	1.87	
S 0169	NP					----	
S 0170	P	11	11			1.90	
S 0171	P	11	11			2.04	
S 0172	P	13	12		1	1.87	
S 0173	P	12	12			1.80	
S 0174	P	14	14			2.07	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 52

Appendix II

Date May 31, 1972

Material Aspirin

Reproduction Data in Hamsters (Individual)

Laboratory No. 0730

Dose 250 mg/kg

Dam No.	Fate*	Implant Sites	Fetuses		Resorption Sites	Average Fetus Weight (g)	Remarks
			Alive	Dead			
A 0151	P	15	15			1.71	
A 0152	P	10	10			1.79	
A 0153	P	14	13		1	2.03	
A 0154	P	15	14		1	1.90	
A 0155	P	15	15			1.79	
A 0156	NP					----	
A 0157	P	14	14			1.71	
A 0158	P	11	10		1	1.85	
A 0159	P	12	12			1.69	
A 0160	P	12	12			1.71	
A 0161	P	10	10			0.90	
A 0162	P	13	13			1.73	
A 0163	P	14	12		2	1.87	
A 0164	P	12	12			1.55	
A 0165	P	12	10		2	1.85	
A 0166	P	11	11			1.82	
A 0167	P	15	14		1	1.54	
A 0168	P	11	11			1.80	
A 0169	P	11	11			1.92	
A 0170	P	11	10		1	1.80	
A 0171	P	10	10			1.67	
A 0172	P	10	10			1.90	
A 0173	P	13	13			1.81	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 57

Appendix II

Date May 31, 1972

Material FDA 71-10

Reproduction Data in Hamsters (Individual)

Laboratory No. 0730 m

Dose 0.3 mg/kg

Dam No.	Fate*	Implant Sites	Fetuses		Resorption Sites	Average Fetus Weight (g)	Remarks
			Alive	Dead			
M 0001	P	12	12			1.84	
M 0002	P	13	13			1.58	
M 0003	P	11	11			1.66	
M 0004	P	13	12		1	1.80	
M 0005	P	11	9		2	1.84	
M 0006	P	12	11		1	1.94	
M 0007	P	10	9		1	1.84	
M 0008	P	8	8			1.74	
M 0009	P	12	10	1	1	1.87	
M 0010	P	12	12			1.67	
M 0011	P	13	13			1.84	
M 0012	P	13	11	2		1.71	
M 0013	P	12	12			1.63	
M 0014	P	9	9			1.73	
M 0015	P	10	9		1	1.87	
M 0016	P	12	12			1.91	
M 0017	P	13	13			1.79	
M 0018	P	13	13			2.02	
M 0019	P	10	8		2	1.77	
M 0020	P	13	12		1	2.06	
M 0021	P	13	12		1	1.73	
M 0022	P	12	12			1.83	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 58

Appendix II

Date May 31, 1972

Material FDA 71-10

Reproduction Data in Hamsters (Individual)

Laboratory No. 0730 m

Dose 1.5 mg/kg

Dam No.	Fate*	Implant Sites	Fetuses		Resorption Sites	Average Fetus Weight (g)	Remarks
			Alive	Dead			
M 0031	NP					----	
M 0032	P	13	12		1	1.97	
M 0033	P	14	14			1.92	
M 0034	P	11	10	1		1.88	
M 0035	P	10	10			2.10	
M 0036	P	12	10	1	1	1.74	
M 0037	P	14	12	1	1	1.92	
M 0038	P	16	16			1.92	
M 0039	P	14	13		1	1.61	
M 0040	P	11	10		1	1.59	
M 0041	P	14	14			1.71	
M 0042	P	14	14			1.70	
M 0043	P	12	12			2.22	
M 0044	P	10	10			1.94	
M 0045	P	12	11		1	1.72	
M 0046	P	13	13			1.90	
M 0047	P	13	11		2	2.00	
M 0048	P	11	11			1.83	
M 0049	P	10	10			1.49	
M 0050	P	11	10		1	1.86	
M 0051	P	12	12			1.87	
M 0052	P	15	13		2	1.40	
M 0053	P	16	16			1.70	
M 0054	P	14	14			1.83	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 59

Appendix II

Date May 31, 1972

Material FDA 71-10

Reproduction Data in Hamsters (Individual)

Laboratory No. 0730 m

Dose 7.0 mg/kg

Dam No.	Fate*	Implant Sites	Fetuses		Resorption Sites	Average Fetus Weight (g)	Remarks
			Alive	Dead			
M 0061	P	15	15			1.81	
M 0062	P	14	14			1.83	
M 0063	P	11	11			2.00	
M 0064	P	10	9		1	2.04	
M 0065	P	13	13			1.77	
M 0066	NP					----	
M 0067	P	13	12		1	1.90	
M 0068	P	14	14			1.95	
M 0069	P	12	12			1.79	
M 0070	P	12	12			1.81	
M 0071	P	10	9		1	1.76	
M 0072	P	12	11		1	1.89	
M 0073	P	10	9		1	1.93	
M 0074	P	13	13			1.71	
M 0075	P	10	9		1	1.75	
M 0076	P	13	13			1.80	
M 0077	P	11	11			1.95	
M 0078	P	11	8		3	1.86	
M 0079	P	14	14			1.99	
M 0080	NP					----	
M 0081	P	12	12			1.92	
M 0082	P	13	13			1.82	
M 0083	P	12	11	1		1.75	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 60

Appendix II

Date May 31, 1972

Material FDA 71-10

Reproduction Data in Hamsters (Individual)

Laboratory No. 0730 m

Dose 32.0 mg/kg

Dam No.	Fate*	Implant Sites	Fetuses		Resorption Sites	Average Fetus Weight (g)	Remarks
			Alive	Dead			
M 0091	P	14	13		1	1.89	
M 0092	P	12	12			1.93	
M 0093	NP					----	Died Day 9.
M 0094	P	12	12			1.81	
M 0095	P	11	11			1.74	
M 0096	P	13	13			1.82	
M 0097	NP					----	
M 0098	P	11	10		1	2.03	
M 0099	NP					----	
M 0100	P	13	13			2.04	
M 0101	P	11	11			1.78	
M 0102	P	10	6		4	1.37	
M 0103	P	12	10		2	2.04	
M 0104	P	10	10			1.87	
M 0105	P	11	7		4	1.83	
M 0106	NP					----	
M 0107	P	10	9		1	2.02	
M 0108	P	15	14		1	1.84	
M 0109	P	12	11		1	1.73	
M 0110	P	14	13		1	1.85	
M 0111	NP					----	
M 0112	P	11	11			1.60	
M 0113	P	12	12			1.88	
M 0114	P	10	10			1.85	
M 0115	P	15	13		2	1.67	
M 0116	P	11	11			1.77	

* P = Pregnant; NP = Not Pregnant

Food and Drug Research Laboratories
INCORPORATED



Maurice Avenue at 58th Street
Maspeth, New York 11378

Telephone: TWining 4-0800
Cable: Foodlabs, New York

**FINAL
REPORT**

Submitted to: DHEW/Public Health Service
Food and Drug Administration CA-272
5600 Fishers Lane-Room 5C-13
Rockville, Maryland 20852

Date July 3, 1972

Laboratory No. 0731 m
Contract No. FDA 71-260

Sample: Light yellow crystalline material

Marking: FDA 71-10 (Potassium nitrite)

Examination Requested: Teratologic evaluation of FDA 71-10 in rabbits

Procedure: (See Appendix I)

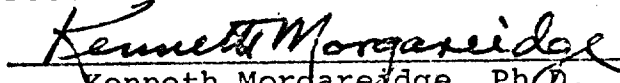
Results: See Tables 1 through 4 and Appendix II

Conclusion: Subject to reexamination in the light of later findings, the following is concluded:

"The administration of up to 23 mg/kg (body weight) of the test material to pregnant rabbits for 13 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls."

Comment: Attention is called to the fact that this is the sixth of a series of reports which will be issued in accordance with terms of the contract cited above. Eventually, a total of at least 36 compounds will have been tested in 18 pairs; each pair being run concurrently against one sham-treated control and one positive control group. Because of the inherent variability of biological data of the type dealt with here, the accumulation and pooling of sequential sets of control values will greatly enhance the statistical value of the findings and the ultimate reliability of the test results.

FOOD AND DRUG RESEARCH LABORATORIES, INC.


Kenneth Morgareidge, Ph.D.
Vice President

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FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 51 & 52; 57 through 60

Material: FDA 71-10

Table 1

Fate Summary
(Rabbits)

Date May 31, 1972

Laboratory No. 0731 m

Group	Material	Dose mg/kg	Total		At Term	
			Mated	Pregnant	Surviving (Total)	Number Pregnant
51	Sham	0	15	10	6	4
52	6-AN*	1.5	15	12	15	12
57	FDA 71-10	0.2	15	13	9	6
58	FDA 71-10	1.1	15	13	8	7
59	FDA 71-10	5.0	15	10	8	6
60	FDA 71-10	23.0	15	11	11	7

* Positive Control: 6 amino nicotinamide dosed on Day 9

Group: 51 & 52; 57 through 60

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Date May 31, 1972Material: FDA 71-10Table 2
Reproduction DataLaboratory No. 0731 m

(Rabbits)

Group:	51	52	57	58	59	60
Dose (mg/kg):	Sham	6-AN**	0.2	1.1	5.0	23.0
Pregnancies						
Total No.	10	12	13	13	10	11
Died or aborted (before Day 29)	9	0	7	7	7	4
To term (on Day 29)	4	12	6	7	6	7
Corpora lutea						
Total No.	186	146	187	196	152	178
Average/dam mated	12.4	9.73	12.5	13.1	10.1	11.9
Live litters						
Total No.*	4	8	5	7	6	5
Implant sites						
Total No. (at term)	29	58	39	40	38	22
Average/dam*	7.25	4.83	6.50	5.72	6.33	3.14
Resorptions						
Total No.*	0	15	14	1	0	5
Dams with 1 or more sites resorbed	--	8	5	1	--	3
Dams with all sites resorbed	--	4	1	0	--	2
Per cent partial resorptions	--	66.7	83.3	14.3	--	42.9
Per cent complete resorptions	--	33.3	16.7	--	--	28.6
Live fetuses						
Total No. (at term)	29	38	25	39	38	17
Average/dam*	7.25	3.17	4.17	5.57	6.33	2.43
Dead fetuses						
Total No.*	0	5	0	0	0	0
Dams with 1 or more dead	--	1	--	--	--	--
Dams with all dead	--	1	--	--	--	--
Per cent partial dead	--	8.33	--	--	--	--
per cent all dead	--	8.33	--	--	--	--
Average fetus weight, g	37.5	30.8	39.7	36.2	36.8	34.8

* Includes only those dams examined at term.

** Positive control: 2.5 mg/kg 6-amino nicotinamide dosed on Day 9.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 51 & 52; 57 through 60

Laboratory No. 0731 m

Table 3

Material FDA 71-10

Date May 31, 1972

Summary of Skeletal Findings
(Rabbits)

Findings	Group No. Dose (mg/kg)	51 Sham	52 6-AN**	57 0.2	58 1.1	59 5.0	60 23.0
Live Fetuses Examined (at term)		29/4	38/8	25/5	39/7	38/6	17/5
Sternebrae							
Incomplete oss.			15/6	2/2	1/1		1/1
Scrambled			1/1				
Bipartite			4/2		3/1		
Fused	1/1		6/4		1/1		2/2
Extra			2/2				3/2
Missing							
Other							
Ribs							
Incomplete oss.							
Fused/split			29/8		1/1		
Wavy							
Less than 12							
More than 13							1/1
Other							
Vertebrae							
Incomplete oss.							
Scrambled			9/3				
Fused							
Extra ctrs. oss.							
Scoliosis							
Tail defects			30/7				
Other							
Skull							
Incomplete closure							
Missing							
Cranioostosis							
Other							
Extremities							
Incomplete oss.			2/1				
Missing							
Extra ; Feet, elongated			1/1				
Miscellaneous							

* Numerator=Number of fetuses affected; Denominator=Number of litters affected

** Positive control: 2.5 mg/kg dosed on Day 9

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 51 & 52; 57 through 60Date May 31, 1972Material FDA 71-10Laboratory No. 0731m

Table 3-a

Summary of Soft Tissue Abnormalities
(Rabbits)

Group	Material	Dose level mg/kg	Dam	Number of Pups	Description
52	6-AN*	1.5	Z 1081	6	Anopia
				2	Club feet
			Z 1082	6	Anopia
				6	Club feet
				6	Cleft palate, hair lip
			Z 1084	5	Anopia
				2	Club feet
			Z 1085	2	Cleft palate, hair lip
				2	Anopia
				2	Craniostenosis
				2	Club feet
			Z 1086	4	Anopia
				4	Club feet
			Z 1088	4	Anopia
				4	Club feet
			Z 1089	6	Anopia
				6	Club feet

* 6 amino nicotinamide (positive control) dosed on Day 9

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 51 & 52; 57 through 60

Date May 31, 1972

Species Rabbits

Table 4

Laboratory No. 0731 m

Average Body Weights*

Group	Material	Dose Level mg/kg	Day				
			0	6	12	18	29**
51	Sham	0	2.48	2.49	2.54	2.55	2.36 (4)
52	6-AN***	1.5	2.28	2.34	2.33	2.36	2.49 (12) ^a
57	FDA 71-9	0.2	2.34	2.37	2.40	2.41	2.48 (6)
58	FDA 71-9	1.1	2.40	2.40	2.31	2.39	2.45 (7) ^a
59	FDA 71-9	5.0	2.19	2.21	2.21	2.27	2.39 (6)
60	FDA 71-9	23.0	2.25	2.28	2.24	2.36	2.49 (7) ^a

* Of pregnant dams

** Number of surviving dams in parentheses (c.f. Table 1)

*** Positive control: 6-amino nicotinamide dosed on Day 9

a) Terminal weight of Z 1090, M 1023, and M 1051 respectively not included in average (c.f. Appendix II)



Appendix I

Teratology Study in Rabbits

Virgin, adult, Dutch-belted female rabbits were individually housed in mesh bottom cages in temperature and humidity-controlled quarters with free access to food and fresh tap water. On Day 0, each doe was given an injection of 0.4 ml of human chorionic gonadotropin (400 IU) via the marginal ear vein. Three hours later, each doe was inseminated artificially with 0.3 ml of diluted semen from a proven donor buck using approximately 20×10^6 motile sperm according to the procedure described by Vogin et al (Pharmacologist 11, 282 (1969)). Beginning on Day 6 and continuing daily through Day 18 the females were dosed with the indicated dosages by oral intubation; the controls were sham treated.

Body weights were recorded on Days 0, 6, 12, 18, and 29 of gestation. All animals were observed daily for appearance and behavior, with particular attention to food consumption and body weight in order to rule out any abnormalities which may have occurred as a result of anorexic effects in the pregnant female animal.

On Day 29 all does were subjected to Caesarean section under surgical anesthesia, and the numbers of corpora lutea, implantation sites, resorption sites and live and dead fetuses were recorded. Body weights of the live pups were also recorded. The urogenital tract of each animal was examined in detail for normality. In addition all fetuses underwent a detailed gross examination for the presence of external congenital abnormalities. The live fetuses of



each litter were then placed in an incubator for 24 hours for the evaluation of neonatal survival. All surviving pups were sacrificed, and all pups examined for visceral abnormalities (by dissection). All fetuses were then cleared in potassium hydroxide (KOH), stained with alizarin red S dye and examined for skeletal defects.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 51

Appendix II

Date May 31, 1972

Material Sham

Reproduction Data in Rabbits (Individual)

Laboratory No. 0731

Dose 0

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead			
S 1076	NP	1	0				--	
S 1077	NP	13	0				--	Died Day 20
S 1078	P	12	2	2			50.2	
S 1079	P	17	5	5			--	Died Day 18
S 1080	P	16	7	7			32.2	
S 1081	P	16	4	4			--	Died Day 24
S 1082	NP	4	0					
S 1083	P	25	11	11			27.7	
S 1084	P	4	1	1			--	Died Day 23
S 1085	P	16	9	9			40.0	
S 1086	NP	10	0					Died Day 12
S 1087	NP	5	0					Died Day 10
S 1088	P	8	2	2				Died Day 11
S 1089	P	18	7	7				Died Day 11
S 1090	P	21	12	12				Died Day 15

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 52

Appendix II

Date May 31, 1972

Material 6-AN

Reproduction Data in Rabbits (Individual)

Laboratory No. 0731

Dose 1.5 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead			
Z 1076	P	6	2			2	--	
Z 1077	NP	4	0				--	
Z 1078	P	8	5	4		1	30.1	
Z 1079	NP	5	0				--	
Z 1080	P	9	1			1	--	
Z 1081	P	13	7	7			33.2	
Z 1082	P	12	6	6			29.2	
Z 1083	P	4	1			1	--	
Z 1084	P	14	10	5	5		36.9	
Z 1085	P	10	5	2		3	27.5	
Z 1086	P	12	6	4		2	26.1	
Z 1087	NP	3	0				--	
Z 1088	P	20	7	4		3	35.7	
Z 1089	P	17	6	6			27.4	
Z 1090	P	9	2			2	--	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 57

Appendix II

Date May 31, 1972

Material FDA 71-10

Reproduction Data in Rabbits (Individual)

Laboratory No. 0731m

Dose 0.2 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead			
M 1001	P	21	14	6		8	46.1	
M 1002	P	13	8	7		1	36.7	
M 1003	P	8	3		3		--	Died Day 29
M 1004	P	21	8	8			--	Died Day 18
M 1005	P	19	2	2			48.0	
M 1006	P	12	6	6				Died Day 11
M 1007	P	16	6	6				Died Day 11
M 1008	P	8	6	6			28.0	
M 1009	P	5	2			2	--	
M 1010	NP	4	0				--	
M 1011	P	14	8	8			--	Died Day 9
M 1012	P	13	6	6			--	Died Day 11
M 1013	P	12	7	4		3	--	
M 1014	P	13	10	10			--	Died Day 11
M 1015	NP	8	0				--	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 58

Appendix II

Date May 31, 1972

Material FDA 71-10

Reproduction Data in Rabbits (Individual)

Laboratory No. 0731m

Dose 1.1 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead			
M 1016	P	18	7	7			--	Died Day 16
M 1017	P	14	1	1			--	Died Day 16
M 1018	NP	14	0				--	Died Day 16
M 1019	P	12	2	2			37.3	
M 1020	P	5	1	1				Died Day 13
M 1021	P	7	2	2				Died Day 9
M 1022	P	11	5	4		1	40.6	
M 1023	P	16	8	8			35.0	
M 1024	P	15	5	5			--	Died Day 12
M 1025	NP	15	0				--	
M 1026	P	22	4	4			37.8	
M 1027	P	11	7	7			31.0	
M 1028	P	17	7	7			35.1	
M 1029	P	12	7	7			36.9	
M 1030	P	7	2	2			--	Died Day 6

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 59

Appendix II

Date May 31, 1972

Material FDA 71-10

Reproduction Data in Rabbits (Individual)

Laboratory No. 0731m

Dose 5.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead			
M 1031	NP	1	0				--	Died Day 8 - Accident
M 1032	P	9	1	1			45.5	
M 1033	NP	3	0				--	
M 1034	P	13	6	6			--	Died Day 17
M 1035	NP	5	0				--	
M 1036	P	12	8	8			32.2	
M 1037	P	27	6	6			38.4	
M 1038	P	16	8	8			32.4	
M 1039	NP	3	0				--	Died Day 12
M 1040	NP	2	0				--	Died Day 10
M 1041	P	19	9	9			36.4	
M 1042	P	7	3	3			--	Died Day 18
M 1043	P	14	6	6			36.0	
M 1044	P	12	4	4			--	Died Day 15
M 1045	P	9	7	7			--	Died Day 11

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 60

Appendix II

Date May 31, 1972

Material FDA 71-10

Reproduction Data in Rabbits (Individual)

Laboratory No. 0731m

Dose 23.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead			
M 1046	NP	9	0				--	
M 1047	P	12	3	1		2	45.9	
M 1048	P	11	5	5				Died Day 16
M 1049	NP	6	0				--	
M 1050	P	9	2			2	--	
M 1051	P	5	1			1	--	
M 1052	P	11	3	3			--	Died Day 12
M 1053	P	14	3	3			--	Died Day 18
M 1054	NP	3	0				--	
M 1055	P	19	5	5			44.2	
M 1056	NP	8	0				--	
M 1057	P	22	2	2			39.2	
M 1058	P	12	3	3			43.6	
M 1059	P	16	6	6			35.9	
M 1060	P	21	1	1			--	Died Day 9

* P = Pregnant; NP = Not Pregnant